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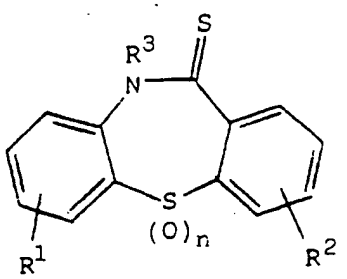

(I)

(57) Abstract

Coumpounds of formula (I) wherein n is 0, 1 or 2; and R^1 and R^2, which may be the same or different, each represent one or more ring substituent(s) selected from: hydrogen, hydroxy, halogen, cyano, nitro, C_{1-6}alkyl, C_{3-6}cycloalkyl or C_{1-6}alkoxy (where the alkyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen atoms and hydroxyl groups); $-NR^4R^5$ where R^4 and R^5, which may be the same or different, each represent hydrogen or C_{1-6}alkyl; $-S(O)_mR^6$, where m is 0, 1, 2 or 3 and R^6 represents hydrogen, C_{1-6}alkyl, or C_{3-6} cycloalkyl: $-SO_2NR^4R^5$ where R^4 and R^5 are each as defined above; phenyl, phenylC_{1-3}alkoxy or phenylC_{1-3}alkyl where the phenyl group may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, nitro, halogen and amino; and $-CO_2H$ or $-COR^7$ where R^7 is C_{1-6} alkyl or C_{3-6}cycloalkyl; R^3 is hydrogen or C_{1-4}alkyl; and esters, salts and other physiologically functional derivatives thereof, show activity as antiviral agents, for example against HIV. The majority of the compounds are noel.

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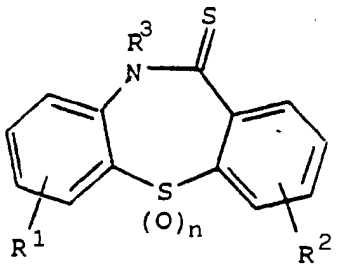
Dibenzothiazepinthione as antiviral agents

The present invention relates to novel dibenzothiazepinthione derivatives and to the use of these and certain related compounds as antiviral agents.

A group of dibenzothiazepinthione derivatives has now been found which show activity as antiviral agents. Thus, according to one aspect, the present invention provides compounds of formula (I)



(I)

wherein:

n is 0, 1 or 2; and

R^1 and R^2, which may be the same or different, each represent one or more ring substituent(s) selected from:

hydrogen, hydroxy, halogen, cyano, nitro, C_{1-6}alkyl, C_{3-6}cycloalkyl or C_{1-6}alkoxy (where the alkyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen atoms and hydroxyl groups);

$-NR^4R^5$ where R^4 and R^5, which may be the same or different, each represent hydrogen or C_{1-6}alkyl;

$-S(O)_mR^6$, where m is 0, 1, 2 or 3 and R6 represents hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

$-SO_2NR^4R^5$ where R^4 and R^5 are each as defined above;

phenyl, phenylC_{1-3}alkoxy or phenylC_{1-3}alkyl where the phenyl group may be optionally substituted by one or more substituents independently

selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, nitro, halogen and amino; and
$-CO_2H$ or $-COR^7$ where R^7 is C_{1-6}alkyl or C_{3-6}cycloalkyl;
R^3 represents hydrogen or C_{1-4}alkyl;
or an ester, salt or other physiologically functional derivative thereof, for use in therapy, more particularly for use as an antiviral agent.

According to one embodiment R^3 represents hydrogen.

As used herein the term "alkyl" as a group or part of a group means a straight or branched chain alkyl group. Such alkyl groups preferably have 1 to 3 carbon atoms and are more preferably methyl or ethyl, most preferably methyl.

The present invention also provides the use of a compound of formula (I) or an ester, salt or other physiologically functional derivative thereof for the manufacture of a medicament for the treatment of a viral infection.

The majority of the compounds of formula (I) are novel. According to a further aspect the invention provides compounds of formula (I) as defined above with the provisos applying to those compounds in which R^3 is hydrogen and n is zero that at least one ring substituent R^1 or R^2 is other than hydrogen and that when there is only a single ring substituent R^1 or R^2 other than hydrogen then this substituent is not a chlorine atom in the 2-, 7-, or 8- position.

According to a yet further aspect the invention provides compounds of formula (I) as defined above with the following provisos applying to those compounds in which R^3 is hydrogen and n is zero:

(1) at least one ring substituent R^1 or R^2 is other than hydrogen;

(2) when there is only a single ring substituent R^1 or R^2 other then hydrogen this is not a chlorine atom in the 2-, 7-, or 8-position;

(3) when there are two ring substituents R^1 and R^2, these are not:

(i) R^1 = 8-chloro; R^2 = 2-chloro; or
(ii) R^1 = 7-iodo; R^2 = 3-dipropylamino.

According to another aspect the invention provides compounds of formula (I) wherein:

n is 0, 1 or 2; and
R^1 and R^2, which may be the same or different, each represent one or more ring substituent(s) selected from:
hydrogen, hydroxy, cyano, C_{1-6}alkyl or C_{3-6}cycloalkyl (where the alkyl or cycloalkyl moiety may be substituted by one or more substituents selected from halogen atoms and hydroxyl groups);
$-NHR^4$ where R^4 represents C_{1-6}alkyl;
$-S(O)_mH$, where m is 0, 1 or 2, or $-SO_3R^6$ where R^6 represents hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;
$-SO_2NR^4R^5$ where R^4 and R^5 are each as defined above;
phenyl, phenylC_{1-3}alkoxy or phenylC_{1-3}alkyl where the phenyl group may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, nitro, halogen and amino; and
$-CO_2H$ or $-COR^7$ where R^7 is C_{1-6}alkyl or C_{3-6}cycloalkyl;
with the provisos that at least one ring substituent R^1 or R^2 is other than hydrogen;
or an ester, salt or other physiologically functional derivative thereof.

Depending on the nature of the substituents R^1 and R^2, centres of optical and geometric isomerism may be introduced into the molecule.

All optical and geometric isomers of compounds of formula (I) and mixtures thereof are embraced by the invention.

According to one preferred embodiment of the present invention, both R^1 and R^2 in formula (I) represent hydrogen atoms.

According to another preferred embodiment of the present invention, the compounds of formula (I) contain ring substituents for example a single ring substituent, R^1 or R^2 selected from halogen, more preferably fluorine or chlorine; nitro; C_{1-6}alkyl, more preferably C_{1-3}alkyl, for example methyl; C_{1-6}alkoxy, more preferably C_{1-3}alkoxy, for example methoxy; haloC_{1-6}alkyl, more preferably haloC_{1-3}alkyl, for example triflouromethyl; $-NR^4R^5$ where R^4 and R^5, which may be the same or different, each represent hydrogen or C_{1-6}alkyl, preferably hydrogen or C_{1-3}alkyl, more preferably both of R^4 and R^5 represent hydrogen or one represents hydrogen and the other represents methyl; $-SO_3H$; phenyl; phenylC_{1-3}alkoxy, preferably phenylmethoxy; or $-CO_2H$.

Ring substituent R^1 or R^2 may be in any one of the 1-, 2-, 3-, 4-, 6-, 7-, 8- or 9-positions. Specific examples of single ring substituents are 1-, 3-or 4-fluoro, 7-chloro, 1-, 2-, 6-, 8- or 9-nitro, 1-, 2-, 6-, 7- or 9-methyl, 1- or 8-methoxy, 1-, 3-, 4- or 7-trifluoromethyl, 1-, 3-, 7- or 8-amino, 1-dimethylamino, 7-SO_3H, 7-phenyl, 1-phenylmethoxy, and 9-CO_2H.

Preferred compounds according to the present invention include:

dibenzothiazepin-11(10H)-thione;
dibenzothiazepin-11(10H)-thione-5,5-dioxide;
3-trifluoromethyldibenzothiazepin-11(10H)-thione;
3-trifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
4-trifluoromethyldibenzothiazepin-11(10H)-thione;
4-trifluoromethyldibenzothiazepin-11(10H)-thione-5-oxide;
4-trifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
7-methoxydibenzothiazepin-11(10H)-thione;

7-methoxydibenzothiazepin-11(10H)-thione-5,5-dioxide;
8-trifluoromethyldibenzothiazepin-11(10H)-thione;
8-trifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
4-trifluoromethyl-9-methyldibenzothiazepin-11(10H)-thione;
4-trifluoromethyl-9-methyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
10-ethyl-3-trifluoromethyldibenzothiazepin-11(10H)-thione;
4-fluorodibenzothiazepin-11(10H)-thione;
4-fluorodibenzothiazepin-11(10H)-thione-5,5-dioxide;
10-methyl-4-fluorodibenzothiazepin-11-thione;
10-methyl-4-trifluoromethyldibenzothiazepin-11-thione;
4-methylthiodibenzothiazepin-11(10H)-thione;
4-methylthiodibenzothiazepin-11(10H)-thione-5,5-dioxide;
2-aminodibenzothiazepin-11(10H)-thione;
2-nitrodibenzothiazepin-11(10H)-thione;
2-nitrodibenzothiazepin-11(10H)-thione-5,5-dioxide;
4,8-bistrifluoromethyldibenzothiazepin-11(10H)-thione;
4,8-bistrifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
1-methoxydibenzothiazepin-11(10H)-thione;
1-methoxydibenzothiazepin-11(10H)-thione-5,5-dioxide;
1-fluorodibenzothiazepin-11(10H)-thione;
methyl dibenzothiazepin-11(10H)-thione-3-carboxylate;
dibenzothiazepin-11(10H)-thione-3-carboxylic acid; and esters, salts and other physiologically functional derivatives thereof, more particularly acid addition salts thereof.

The compounds of formula (I) as defined above have been found to show antiviral activity in a number of assays, for example against Varicella-Zoster virus, Human cytomegalovirus, Human hepatitis virus, for example hepatitis B, and against Human T-cell lymphotropic viruses, especially HIV-1. The compounds of formula (I) may thus be useful in the treatment of a human or animal subject suffering from or liable to suffer from a viral infection. As used herein, reference to treatment includes both therapeutic and prophylactic treatment. The compounds of formula (I) may be particularly useful in the treatment

of a human or animal subject suffering from or liable to suffer from a disorder associated with HIV infection, for example AIDS.

According to another aspect, the present invention provides a method of treatment of a human or animal subject suffering from or liable to suffer from a viral infection which comprises administering an effective amount of a compound of formula (I) or an ester, salt or other physiologically functional derivative thereof. According to a particular embodiment of this aspect of the invention, the viral infection is an HIV infection.

The present invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or an ester, salt or other physiologically functional derivative thereof. The pharmaceutical composition is formulated in a manner suitable for use in human or veterinary medicine and for administration by any convenient route. The pharmaceutical composition will generally contain at least one physiologically acceptable carrier or excipient in addition to the active ingredient.

As used herein, the term "physiologically functional derivative" means any physiologically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) such a compound or an antivirally active metabolite or residue thereof.

Preferred esters of the compounds of formula (I) included within the scope of the invention as physiologically functional derivatives include carboxylic acid esters in which the non-carbonyl moiety of the ester grouping is selected from straight or branched chain alkyl (for example methyl, n-propyl, n-butyl or t-butyl), cycloalkyl, alkoxyalkyl (for example methoxymethyl), aralkyl (for example benzyl), aryloxyalkyl (for example phenoxymethyl), aryl (for example phenyl optionally substituted by, for example, halogen, C_{1-4}alkyl, C_{1-4}alkoxy

or amino): sulphonate esters such as alkyl- or alkylarylsulphonyl (for example methanesulphonyl); amino acid esters (for example L-valyl or L-isoleucyl); and mono-, di- or tri-phosphate esters. In such esters unless otherwise specified, any alkyl moiety present advantageously contains 1 to 18 carbon atoms, particularly 1 to 6 carbon atoms, more particularly 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. Any reference to any of the above compounds also includes a reference to physiologically acceptable salts thereof.

Examples of physiologically acceptable salts of the compounds of formula (I) and physiologically acceptable derivatives thereof include salts derived from an appropriate base, such as alkali metal (for example sodium), alkaline earth metal (for example magnesium) salts, ammonium and NX_4^+ (wherein X is C_{1-4}alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulphonic, ethanesulphonic, benzenesulphonic and p-toluenesulphonic acids and inorganic acids such as hydrochloric, sulphuric, phosphoric and sulphamic acids. Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+, NH_4^+, and NX_4^+ (wherein X is a C_{1-4}alkyl group).

For therapeutic use, salts of compounds of formula (I) will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example in the preparation or purification of the compound. All salts whether or not derived from a physiologically acceptable acid or base are to be considered as being within the scope of the present invention.

The compounds according to the invention may be employed in combination with other therapeutic agents for the treatment of viral infections or related conditions. Examples of such further therapeutic agents include other agents which are effective for the treatment of HIV infections or associated conditions such as 3'-azido-3'-deoxythymidine (zidovudine), other 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine and 2',3'-dideoxyinosine, carbovir, acyclic nucleosides (e.g. acyclovir), 2',3'-didehydrothymidine, chloro-TIBO, HEPT derivatives, Pentamidine, hydroxynaphthoquinones, phosphonate derivatives of nucleosides e.g. PMEA, interferons such as α-interferon, renal excretion inhibitors such as probenicid, nucleoside transport inhibitors such as dipyridamole, as well as immunomodulators such as interleukin II and granulocyte macrophage colony stimulating factors, erythropoetin, phosphonoformic acid and soluble CD_4 and genetically engineered derivatives thereof. The component compounds of such combination therapy may be administered simultaneously, in either separate or combined formulations, or at different times, e.g. sequentially, such that a combined effect is achieved.

The compounds of formula (I), also referred to herein as active ingredients, may be administered for therapy by any suitable route including oral, rectal, nasal, topical (including buccal and sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intravenous and intradermal) and pulmonary. It will also be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the infection and the chosen active ingredient.

In general a suitable dose for treatment of a viral infection such as HIV is in the range of 0.5 to 120 mg per kilogram body weight of the recipient per day, preferably in the range of 1 to 90 mg per kilogram body weight per day and most preferably in the range 2 to 60 mg per kilogram body weight per day. The desired dose is preferably presented as two, three, four, five, six or more sub-doses

administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 1 to 1500 mg, preferably 5 to 1000 mg, and most preferably 10 to 700 mg of active ingredient per unit dosage form.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.1 to about 100 1M, preferably about 0.5 to 70 1M, most preferably about 1 to about 50 1M. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or orally administered, for example, as a tablet, capsule or syrup containing about 0.5 to about 100 mg/kg of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient.

While it is possible for the active ingredient to be administered alone it is preferable to present it as a pharmaceutical formulation comprising at least one compound of formula (I), together with one or more pharmaceutically acceptable carriers or excipients. The composition may optionally contain one or more other therapeutic agents. Each carrier and/or must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intravenous and intradermal) and pulmonary adminstration. The formulations may conveniently be presented in unit dosage form and may be prepared by any known methods in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into

association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, crossed-linked sodium carboxmethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration in tho mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical compositions for topical administration according to the present invention may be formulated as an ointment, cream, suspension, lotion, powder, solution, paste, gel, spray, aerosol or oil. Alternatively, a formulation may comprise a dressing such as a bandage or adhesive plaster impregnated with active ingredients and optionally one or more excipients or diluents. Carriers which may be used include for example polyhydric alcohols such as polyethylene glycols, propylene glycol or glycerol. Suitable excipients are those known in the art to be appropriate.

Formulations for rectal administration may be presented as suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injections solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient: and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

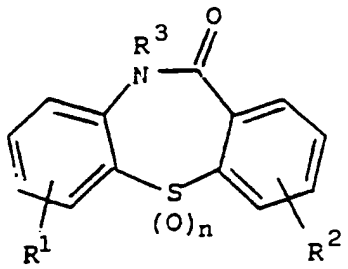
Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavouring agents.

The compounds according to the invention may also be presented for the use in the form of veterinary formulations, which may be prepared, for example, by methods that are conventional in the art.

According to another aspect, compounds of formula (I) may be prepared by the general methods outlined below. In the following description the symbols R^1, R^2 and n have the meanings ascribed to them in formula (I) unless otherwise stated.

According to a first general process (A), compounds of formula (I) can be prepared by reaction of the corresponding thiazepinone of formula (II)



(II)

with a thionating agent, for example phosphorus pentasulphide (P_4S_{10}) or 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4,diphosphetane-2,4-disulphide (Lawesson's Reagent). The reaction is generally carried out under standard conditions for the use of the thionating agent in question (see for example Synthesis, 1979, page 941; Tet. Lett., 3015 (1983); Bull. Soc. Chim. Belg., 86, 321 (1977); J. Het. Chem., 25, 97 (1988); Tet. Lett., 25(32), 3457 (1984)).

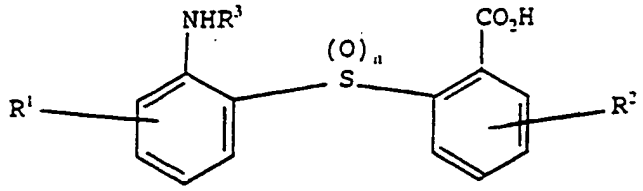
For example, a compound of formula (II) may be dissolved in a suitable solvent such as pyridine and stirred vigorously with the thionating agent, e.g. P_4S_{10}, under an inert gas such as nitrogen. The mixture may then be stirred and refluxed under the inert gas for several hours, e.g. about 6 to 11 hours, and then left for a further similar period before working up.

According to a second general process (B), compounds of formula (I) in which n is 1 or 2 can be prepared by treating the corresponding compound in which n is zero with an appropriate oxidising agent. Suitable oxidising agents include m-chloroperoxy benzoic acid (MCPBA), sodium perborate, NO_2BF_4 (J. Amer. Chem. Soc., 101, 5317 (1979)), ruthenium/alumina (Tet. Lett. 785 (1976)) and nitric acid (J. Org. Chem., 26, 1331 (1961)).

The conditions of the oxidation can be adjusted depending on the desired product. Thus, for example, a compound of formula (I) can be converted into the corresponding sulphoxide (n = 1) by treatment with about 1 equivalent of MCPBA in a suitable solvent such as chloroform. The reaction can be carried out at room temperature and is complete in a relatively short period of say about half an hour. The corresponding sulphone (n = 2) can be produced under similar conditions except that about 2 equivalents of MCPBA are used and the reaction is continued for a longer period of time, say about 24 hours. Alternatively a compound of formula (I) can be converted into the corresponding sulphone by treatment with an excess of sodium perborate in a suitable solvent, e.g. acetic acid.

According to a third general process (C), compounds of formula (I) in which R^3 is C_{1-4}alkyl can be prepared by treating the corresponding compound of formula (I) in which R^3 is hydrogen with an appropriate alkylating agent. Suitable alkylating agents include alkyl halides, for example alkyl iodides. The reaction may be carried out in the presence of base, for example sodium hydride, in a suitable solvent such as an amide, for example dimethylformamide, at a temperature of for example 0 to 50°C, preferably ambient temperature.

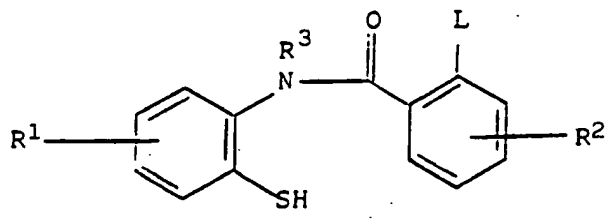
According to a first general process (1) thiazepinones of formula (II) can be prepared by cyclisation of the corresponding 2-(2-carboxyphenylthio)aniline derivative of formula (III)



(III)

This process is particularly applicable to the production of compounds in which R^3 is hydrogen. The reaction can be carried out at elevated temperature, for example 110°C or above, more particularly 110 to 160°C, optionally in the presence of a suitable solvent, for example an inert solvent such as toluene, xylene or quinoline. For example, the reaction may be carried out in refluxing xylene fractions of boiling point 130 to 140°C. If desired the carboxylate group can be activated prior to the cyclisation, for example by the use of a reagent such as dicyclohexylcarbodiimide or a water soluble diimide.

According to a second general process (2), thiazepinones of formula (II) in which n is zero can be prepared by cyclisation of a compound of formula (IV)



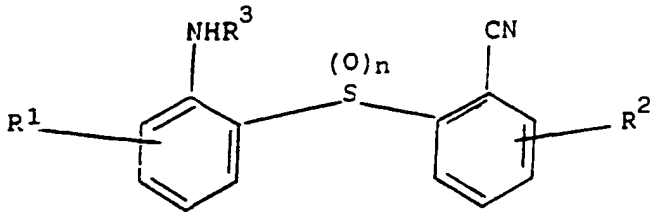
(IV)

where L is a leaving group such as halogen, e.g. -F, -Cl, -Br or -I, $-NO_2$ or $-SO_2R$ where R is alkyl or aryl. This process is particularly applicable to the production of compounds in which R^3 is hydrogen. The reaction may be carried out by treatment with base, for example sodium carbonate, triethylamine, 1,8-diazabicyclo[5,4,0]-undec-7-ene or sodium hydride, in a suitable solvent such as tetrahydrofuran or dimethylformamide, optionally at elevated temperature, for example 60 to 120°C. Particularly in the case where the group L is halogen, the reaction may be carried out in the presence of a copper (Cu(0), Cu(I) or Cu(II)) catalyst.

According to a third general process (3), thiazepinones of formula (II) in which n is 1 or 2 can be prepared by treating the corresponding compound in which n is zero with an appropriate oxidising agent. Suitable reaction conditions are, for example, the conditions that are described above for the oxidation of a compound of formula (I) in which n is zero.

According to a fourth general process (4), compounds of formula (II) in which R^3 is C_{1-4}alkyl can be prepared from the corresponding compound of formula (II) in which R^3 is hydrogen by treatment with an appropriate alkylating agent in the manner described above for process (C).

Compounds of formula (III) can be prepared by hydrolysis of a corresponding 2-(2-aminophenylthio)-benzonitrile of formula (V)

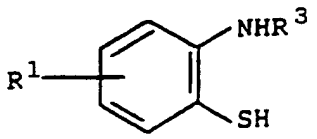


(V)

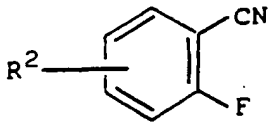
Hydrolysis may be carried out in the presence of an acid, for example a mineral acid such as sulphuric acid, and/or an organic acid such as acetic acid. For example the reaction may be carried out in a 1:1:1 (v/v/v) mixture of acetic acid, water and conc sulphuric acid under reflux, for example for about 4 to 8 hours. Alternatively, the hydrolysis may be carried out in the presence of a base, such as an alkali metal hydroxide, e.g. sodium or potassium hydroxide. For example, the reaction may be carried out by refluxing in aqueous solution, for example over a period of about 4 to 14 hours.

Compounds of formula (V) in which n is 1 or 2 may be prepared by oxidation of compounds of formula (V) in which n is zero, for example under the conditions described above for the oxidation of compounds of formula (I) in which n is zero.

Compounds of formula (V) can be prepared by treating the appropriate 2-aminothiophenol of formula (VI) with the appropriate 2-fluorobenzonitrile of formula (VII).



(VI)



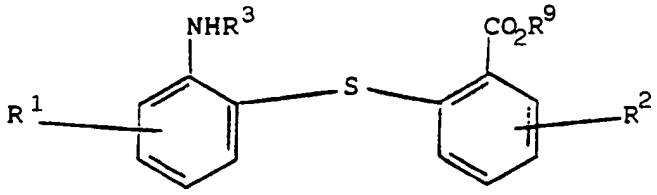
(VII)

The reaction may be carried out in the presence of base, for example an alkali metal hydride, alkali metal hydroxide, alkali metal alkoxide or pyridine, preferably in a suitable solvent, for example an ether

such as tetrahydrofuran, an alcohol, dimethyl formamide, pyridine or water.

Where they are not already known, compounds of formula (VI) can be prepared by standard methods (see for example Ann., 588, 29 (1947)).

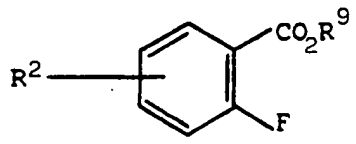
Alternatively, compounds of formula (III) can be prepared by hydrolysis of the corresponding carboxylic acid ester of formula (VIII)



(VIII)

where R^9 is an alkyl group, preferably ethyl. The reaction can be carried out under standard conditions for the hydrolysis of a carboxylic acid ester, for example treatment with a base such as sodium hydroxide in a suitable solvent such as aqueous ethanol. The reaction may be carried out at elevated temperature such as 80 to 100°C.

The ester of formula (VIII) can be prepared by reaction of an appropriate 2-aminothiophenol (VI) with an appropriate 2-fluorobenzoic acid ester (IX)

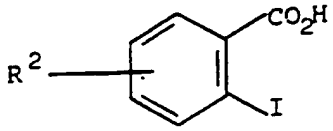


(IX)

under conditions analogous to those described above for the reaction of compounds of formulae (VI) and (VII).

The ester of formula (IX) can be prepared from the corresponding 2-fluorobenzoic acid by standard esterification techniques.

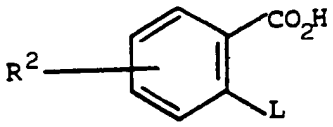
As a further alternative, compounds of formula (III) can be prepared by reaction of an appropriate 2-aminothiophenol (VI) with a 2-iodobenzoic acid derivative of formula (X).



(X)

The reaction is preferably carried out in the presence of a base, for example an alkali metal hydroxide such as potassium hydroxide, and a copper catalyst, e.g. Cu, CuO or CuCl. The reaction may be carried out in water at elevated temperature, e.g. about 100°C, or in a suitable organic solvent such as quinoline.

Compounds of formula (IV) can be prepared by reaction of a suitable 2-aminothiophenol of formula (VI) with a benzoic acid derivative of formula (XI)



(XI)

or an activated derivative thereof such as the corresponding acid chloride or anhydride. The reaction can be carried out in a suitable solvent such as pyridine at elevated temperature, e.g. about 100°C.

Where it is desired to isolate a compound of formula (I) as an acid addition salt, for example a physiologically acceptable acid addition salt, the salt may be formed by reacting the compound of formula (I)

in the form of the free base with the appropriate acid. The two reactants are preferably used in equivalent amounts and the reaction may be carried out in a suitable solvent such as an alcohol, for example ethanol, an ester, for example ethyl acetate, or an ether, for example tetrahydrofuran. One salt of a compound of formula (I) may be converted into another salt using standard methods, for example where it is desired to convert a salt of a compound of formula (I) with an acid which is not physiologically acceptable into a salt with a physiologically acceptable acid.

The invention is further illustrated by the following examples.

Example 1

3-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

(a) 2-(2-Aminophenylthio)-4-trifluoromethylbenzonitrile

2-Aminothiophenol (8.17g, 65mmol) was added to a mixture of sodium hydride (2.35g of 80% dispersion, 1.2 eq) in dimethylformamide (DMF, 100 ml) at 0°C under a nitrogen atmosphere. After stirring for 30 mins 2-fluoro-4-trifluoromethylbenzonitrile (11.68g, 0.95 eq) was added and the reaction mixture stirred at 0°C for 1 hr then kept at 10°C overnight. The solvent was evaporated in vaccuo and the residue taken up in ether (100 ml) and washed with sodium bicarbonate solution (1 M, 100 ml). The organic layer was separated and dried (sodium sulphate, Na_2SO_4), and evaporated to give a yellow solid. The title compound (12.5g, m.p. 102-104°C, Rf 0.67, hexane/EtOAc 2:1) was obtained in pure form by chromatography on silica eluting first with hexane/ethyl acetate (6:1) then (4:1).

(b) 3-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4] thiazepin-11-one

2-(2-Aminophenylthio)-4-trifluoromethylbenzonitrile (12.5g, 42.5 mmol) in glacial acetic acid (135 ml), water (135 ml), and concentrated sulphuric acid (135 ml) was heated to 125-130°C for 2.5 hr before being cooled and added to 1.5 l of ice-water and adjusted to pH 4 with sodium hydroxide solution (10N, 480 ml). The product was extracted into chloroform (1l), dried (Na_2SO_4) and evaporated in vacuo. The light brown oil was placed in xylene (800 ml) and refluxed for 18 hr in a Dean-Stark apparatus. The title compound was obtained as off-white crystals (7.8g. m.p. 216-217°C, Rf 0.28, hexane/EtOAc 2:1) after reducing the volume to appproximately 450 ml and allowing the solution to cool.

(c) 3-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4] thiazepin-11-thione

Phosphorus pentasulphide (2.25g) was added to a solution of 3-trifluoromethyl-9,10-dihydrodibenzo [b,f][1,4]thiazepin-11-one (2g, 6.8 mmol) in pyridine (30 ml) and the mixture heated under reflux for 6.5 hr. The mixture was allowed to cool and then poured into warm water (100 ml) with stirring. Filtration of the cooled mixture and recrystallisation from ethanol gave the title compound as yellow needles (1.68g, m.p. 236-239°C, Rf 0.58, hexane/EtOAc 2:1).

Example 2

3-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione-5,5-dioxide

(a) 3-Trifluoromethyl-9,10-dihydrodibenzo[b,f][1,4]thiazepin-11-one-5,5-dioxide

Metachloroperoxybenzoic acid (MCPBA, >2 eq) was added to a solution of the 3-trifluoromethyl-9,10-dihydrodibenzo

[b,f][1,4]thiazepin-11-one (110 mg, 0.37 mmol) in dichloromethane and then stirred at room temperature overnight. Sodium bicarbonate (1 M, 10 ml) and dichloromethane (10 ml) were added and the organic layer separated and dried (Na_2SO_4). Evaporation and chromatography on silica, eluting with cyclohexane/ethyl acetate, and trituration of the product with hexane/ethyl acetate (4:1) gave the title compound as an off-white powder (50 mg, m.p. 240-241°C, Rf 0.5, hexane/EtOAc 1:1).

(b) 3-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione-5,5-dioxide

Phosphorus pentasulphide (1g) was added to a solution of 3-trifluoromethyl-9,10-dihydrodibenzo [b,f][1,4]thiazepin-11-one-5,5-dioxide (1g, 3 mmol) in pyridine (20 ml) and heated under reflux for 6.5 hr. A further 500 mg of phosphorus pentasulphide was added and the mixture heated for a further 6 hr before being allowed to cool overnight. The mixture was added to hot water (100 ml) with stirring. Filtration of the cooled mixture and recrystallisation from ethanol gave the title compound as a yellow solid (650 mg, m.p. 275-278°C, Rf 0.4, hexane/EtOAc 2:1).

Example 3

10,11-Dihydrodibenzo[b,f][1,4]thiazepin-11-thione

(a) 2-(2-Aminophenylthio)benzonitrile

2-Aminothiophenol (6.26g, 50 mmol) was dissolved in dry THF (50 ml) and sodium hydride (2g of 60% dispersion, 1 eq) added with stirring at 0°C under nitrogen. After stirring for 0.5 hr this mixture was added portionwise to a stirred solution of 2-fluorobenzonitrile (1eq) in THF (30 ml). The mixture was allowed to warm to room temperature overnight and then evaporated in vacuo and the residue purified by chromatography on silica,

eluting with dichloromethane. The title compound was obtained as an off-white solid (5.27g).

(b) 10,11-Dihydrodibenzo[b,f][1,4]thiazepin-11-one

2-(2-Aminophenylthio)benzonitrile (3.72g, 16 mmol) was dissolved in water (35 ml), acetic acid (35 ml) and concentrated sulphuric acid (35 ml) and stirred and heated under reflux for 3 hr. The mixture was allowed to cool and poured onto crushed ice (600 ml) and adjusted to pH 6 with sodium hydroxide solution (10 N). The product was extracted into dichloromethane (700 ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in xylene (250 ml) and refluxed in a Dean-Stark apparatus for 72 hr. Filtration of the cold reaction mixture and recrystallisation from ethanol gave the title compound as a white crystals (2.99g, m.p. 255-256^{o}C, Rf 0.68, CH_2Cl_2/MeOH 19:1).

(c) 10,11-Dihydrodibenzo[b,f][1,4]thiazepin-11-thione

Phosphorus pentasulphide (1.2 eq) was added to a solution of 10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one (1.14g, 5 mmol) in pyridine (40 ml) and heated under reflux for 15 hr. The mixture was allowed to cool and poured into hydrochloric acid (1.3 M) at 0^{o}C. Filtration of the yellow precipitate and purification by chromatography on silica (eluting with dichloromethane/methanol, 99:1) followed by recrystallisation from ethanol gave the title compound as yellow crystals (700 mg, m.p. 245-246^{o}C, Rf 0.81, CH2Cl2/MeOH 9:1).

Example 4

8-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

(a) 8-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4] thiazepin-11-one

Using a procedure analagous to that of Example 3(a) and (b), 4-trifluoromethyl-2-aminothiophenol hydrochloride (11.48 g, 50 mmol) was combined with 2-fluorobenzonitrile in DMF solvent (100 ml) to give crude 2-(4-trifluoromethyl-2-aminophenylthio) benzonitrile (6.84g). Hydrolysis and subsequent condensation gave the title compound as off-white crystals from ethanol (1.1g, m.p. 233-235°C, Rf 0.21, CH_2Cl_2/MeOH 50:1).

(b) 8-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

Phosphorus pentasulphide (0.6 g, 2.5 mmol) was added to a stirred solution of 8-trifluoromethyl-9,10-dihydrodibenzo [b,f][1,4]thiazepin-11-one (0.295g, 1 mmol) in pyridine (10 ml). The mixture was heated under reflux for 6 hr and then at room temperature overnight. A further 0.3 g of phosphorous pentasulphide was added and the reaction mixture refluxed for 6 hr and then left at room temperature overnight before hot water (40 ml) added. Filtration and recrystallisation from toluene then ethanol gave he title compound as fine yellow needles (0.22 g, m.p. 232-233°C, Rf 0.76, petrol/EtOAc 2:1).

Example 5

4-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

(a) 3-Trifluoromethyl-2-(2-aminophenylthio)benzonitrile

Using a procedure analagous to that of Example 3(a), 2-aminothiophenol (6.26 g, 50 mmol) was combined with 3-trifluoromethyl-2-fluorobenzonitrile (1 eq) in DMF solvent (50 ml) to give the title compound as a white solid from cyclohexane (10.41 g).

(b) 4-Trifluoromethyl-10,11-dihydrodibenzo[b,f][1,4] thiazepin-11-one

3-Trifluoromethyl-2-(2-aminophenylthio)benzonitrile (7.36 g, 25 mmol) was dissolved in acetic acid (80 ml), water (80 ml) and concentrated sulphuric acid (80 ml) and the mixture stirred and heated under reflux for 5 hr, then at room temperature for 15 hr. The mixture was poured onto crushed ice (500 ml) and adjusted to pH 4 with sodium hydroxide (10 N). The mixture was extracted with dichloromethane, dried ($MgSO_4$) and evaporated and the residue dissolved in hot xylene (500 ml). The mixture was heated under reflux for 21 hr in a Dean-Stark apparatus before being allowed to cool. After chromatography on silica (ethyl acetate/petrol eluant) and recrystallisation from cyclohexane the title compound was obtained as white crystals (3.99 g, m.p. 256-258°C, Rf 0.44, petrol/EtOAc 1:1).

(c) 4-Trifluoromethyl-9,10-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

Phosphorus pentasulphide (0.6 g, 2.5 mmol) was added to a stirred solution of 4-trifluoromethyl-9,10-dihydrodibenzo[b,f][1,4]thiazepin-11-one (0.59 g, 2 mmol) in pyridine (20 ml). The mixture was heated under reflux for 6.5 hr and then at room temperature overnight before hot water (40 ml) added. Filtration and recrystallisation from ethanol gave the title compound as fine yellow needles (0.503 g, m.p. 265-267°C, Rf 0.65, petrol/EtOAc 1:1).

Example 6

2-Nitro-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

(a) 2-(2-Aminophenylthio)-5-nitrobenzonitrile

2-Aminothiophenol (6.26g, 50mmol) was added to a mixture of sodium hydride (2.0g of 60% oil dispersion, 50mmol) in DMF (100ml) at 0° under nitrogen. After stirring for 30 minutes at

0°, 2-fluoro-5-nitrobenzonitrile (8.3g, 50mmol) in DMF (20ml) was added and the mixture kept at room temperature overnight. The reaction mixture was evaporated and azeotroped with toluene, then the residue was partitioned between chloroform and water and the layers separated. Drying (sodium sulphate) and evaporation of the organic layer gave a residue which was separated from chloroform as bright yellow crystals (10.1g, Rf 0.52 in 1:1 ethyl acetate/hexane).

(b) 2-Nitro-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one

2-(2-Aminophenylthio)-5-nitrobenzonitrile (8.5g, 25mmol) was dissolved in a mixture of glacial acetic acid (80ml), concentrated sulphuric acid (100ml) and water (80ml) and then heated under reflux for 6 hours. The cooled mixture was added to ice water (500ml) and brought to pH 4 by addition of 10N aqueous sodium hydroxide. Extraction with dichloromethane followed by filtration, drying (sodium sulphate) and evaporation of the organic layer afforded a residue which was put into xylene (500ml) and refluxed for 15 hours with azeotropic removal of water. On cooling a brown powder deposited which was filtered off and purified by chromatography on silica gel eluting with 1:1 v/v ethyl acetate-hexane. Recrystallisation from ethanol gave the product as a greyish powder (2.80g, m/s, M^+ = 272).

(c) 2-Nitro-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

2-Nitro-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one (0.27g) was dissolved in toluene (20ml). Phosphorus pentasulphide (0.22g) was added to the solution and the whole was stirred under reflux for 4 hours, then cooled and left overnight. Addition of water (40ml) and separation of the phases gave, after evaporation of the dried organic layer, a yellow solid which was purified by column chromatography on silica gel and recrystallisation from

ethanol to give the product as yellow needles (0.22g, m/s. M^+ = 288).

Example 7

2-Amino-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

(a) 2-Amino-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one

2-Nitro-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one (0.82g) was dissolved in warm acetic acid (100ml) and the resulting solution hydrogenated over Adam's catalyst (80mg) for 3 hours at atmospheric pressure. The catalyst was filtered off and the solution evaporated to dryness. Recrystallisation of the residue from methanol gave the product as a greenish powder (0.48g, m/s, M^+ = 242).

(b) 2-Amino-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

2-Amino-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one (0.12g) was dissolved in toluene (20ml). Phosphorus pentasulphide (0.11g) was added to the solution and the whole was stirred under reflux for 16 hours and then cooled. Addition of water (40ml) and separation of the phases gave, after evaporation of the dried organic layer, a yellow solid which was purified by column chromatography on silica gel and recrystallisation from ethanol to give the product as yellow needles (0.22g, m/s. M^+ = 258).

Example 8

(i) 4,8-Bis(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4] thiazepin-11-thione

(a) 2-(2-Amino-4-trifluoromethylphenylthio)-3-trifluoromethyl-benzonitrile

2-Amino-4-trifluoromethylthiophenol (5.74g, 25mmol) was added to a mixture of sodium hydride (2.0g of 60% oil dispersion, 50mmol) in DMF (100ml) at 0° under nitrogen. After stirring for 30 minutes at 0°, 2-fluoro-3-trifluoromethylbenzonitrile (4.73g, 25mmol) in DMF (20ml) was added and the mixture kept at room temperature overnight. The reaction mixture was evaporated and azeotroped with toluene, then the residue was partitioned between chloroform and water and the layers separated. Drying (magnesium sulphate) and evaporation of the organic layer gave a residue which was purified by chromatography on silica gel, eluting with dichloromethane. Recrystallisation from cyclohexane afforded the product as colourless needles (6.44g).

(b) 4,8-Bis(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]-thiazepin-11-one

2-(2-Amino-4-trifluoromethylphenylthio)-3-trifluoromethylbenzonitrile (5.43g, 15mmol) was dissolved in a mixture of glacial acetic acid (60ml), concentrated sulphuric acid (55ml) and water (60ml) and then heated under reflux for 8 hours. The cooled mixture was added to ice water (500ml) and brought to pH 4 by addition of 10N aqueous sodium hydroxide. Extraction with dichloromethane followed by filtration, drying (sodium sulphate) and evaporation of the organic layer afforded a residue which was put into xylene (500ml) and refluxed for 72 hours with azeotropic removal of water. The resulting solution was evaporated and the residue was recrystallised twice from ethanol to give the product as colourless needles (4.30g, m/s, M^+ = 363).

(c) 4,8-Bis(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]-thiazepin-11-thione

4,8-Bis(trifluoromethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepin 11-one (0.54g) was dissolved in pyridine (15ml). Phosphorus pentasulphide (0.60g) was added to the solution and the whole was

stirred under reflux for 6 hours, then cooled and left overnight. Addition of water (40ml) and cooling gave a yellow solid which was filtered off, washed with water and recrystallised from ethanol to give the product as yellow needles (0.26g, m/s. M^+ = 379).

(ii) 9-Methyl-4-trifluoromethyl-10,11-dihydrobenzo[b,f][1,4]-thiazepin-11-thione

(a) 9-Methyl-4-trifluoromethyl-10,11-dihydrobenzo[b,f][1,4]-thiazepin-11-one

Similarly prepared as in (i) from 3-methyl-2-aminothiophenol. Product obtained from toluene as fawn needles (m/s, M^+ = 309).

(b) 9-Methyl-4-trifluoromethyl-10,11-dihydrobenzo[b,f][1,4]-thiazepin-11-thione

Similarly prepared as in (i) from 9-methyl-4-trifluoromethyl-10,11-dihydrobenzo[b,f][1,4]thiazepin-11-one. Product obtained from ethanol as yellow needles (m.p. 265 - 267°).

(iii) 1-Methoxy-10,11-dihydrobenzo[b,f][1,4]thiazepin-11-thione

(a) 1-Methoxy-10,11-dihydrobenzo[b,f][1,4]thiazepin-11-thione

Similarly prepared as in (i) from 2-aminothiophenol and 2-fluoro-6-methoxybenzonitrile. Product obtained from ethanol as pale yellow crystals (m/s, M^+ = 258).

(b) 1-Methoxy-10,11-dihydrobenzo[b,f][1,4]thiazepin-11-thione

Similarly prepared as in (i) from 1-methoxy-10,11-dihydrobenzo-[b,f][1,4]thiazepin-11-one. Product obtained from ethanol as fine yellow needles (m/s. M^+ = 273).

(iv) 4-Fluoro-10,11-dihydrobenzo[b,f][1,4]thiazepin-11-thione

(a) 4-Fluoro-10,11-dihydrobenzo[b,f][1,4]thiazepin-11-one

Similarly prepared as in (i) from 2-aminothiophenol and 2,3-difluorobenzonitrile. Product obtained from ethanol as pale yellow crystals (m/s, M^+ = 245).

(b) 4-Fluoro-10,11-dihydrobenzo[b,f][1,4]thiazepin-11-thione

Similarly prepared as in (i) from 4-fluoro-10,11-dihydrobenzo-[b,f][1,4]thiazepin-11-one. Product obtained from ethanol as fine yellow needles (m/s, M^+ = 261).

Example 9

10-Ethyl-3-trifluoromethyl-10,11-dihydrobenzo[b,f][1,4]-thiazepin-11-thione

(a) 10-Ethyl-3-trifluoromethyl-10,11-dihydrobenzo[b,f][1,4]-thiazepin-11-one

3-Trifluoromethyl-10,11-dihydrobenzo [b,f][1,4]thiazepin-11-one (0.50g) in DMF (15ml) was treated with sodium hydride (80% oil dispersion, 0.12g) at 50^0 for 10 minutes under nitrogen. The solution was cooled to room temperature and ethyl iodide was introduced. After a further 1 hour the solvent was removed by evaporation and the residue partitioned between ethyl acetate and dilute aqueous sodium bicarbonate. Evaporation of the dried organic layer gave a residue which was crystallised from hot ethanol to give the product as white needles (m.p. 124 - 125^0).

(b) 10-Ethyl-3-trifluoromethyl-10,11-dihydrobenzo[b,f][1,4]-thiazepin-11-thione

10-Ethyl-3-trifluoromethyl-10,11-dihydrobenzo[b,f][1,4]thiazepin-11-one (0.30g) and phosphorus pentasulphide (0.60g) were heated together in pyridine (6ml) for 24 hours after which the mixture was poured into water and cooled. The resulting precipitate was filtered off and the product purified by silica gel chromatography eluting with hexane/ethyl acetate (6:1, v/v) followed by recrystallisation from ethanol to give the product as yellow needles (0.12g, m.p. 155 - 156°).

Example 10

7-Methoxy-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

(a) 5-[(2-Amino-5-methoxy)phenyl]-2-mercaptobenzoic acid

To 2-amino-6-methoxy-1,3-benzthiazole (5g, 0.027M) was added a solution of potassium hydroxide (25g in 50 ml of water). The mixture was heated at 140° for 5 hours. The crude 2-amino-5-methoxybenzenethiol produced was diluted with water (150ml) and to this was added copper powder (1.25g, 1 equivalent) and iodobenzoic acid (6.8g, 1 equivalent). The mixture was heated under reflux for 4 hours under nitrogen. On cooling the mixture was filtered to remove copper, and acidified with concentrated hydrochloric acid. The solution was filtered to give the product as a light green solid (5g).

(b) 7-Methoxy-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one

To 5-[(2-amino-5-methoxy)phenyl]-2-mercaptobenzoic acid (2g, 8.3mmol) in pyridine (50ml) was added dimethylaminopropylcarbodiimide (1.68g, 1.2 equivalents) and the mixture was heated under reflux for 1.5 hours. The pyridine was removed under reduced pressure, and the residue was washed with 10% hydrochloric acid, filtered, the solid washed with water and recrystallised from methanol to give the title compound as a blue solid (1.83g, m.p.

232 - 234°, Rf 0.51 [silica, cyclohexane/ethyl acetate, 1:1 v/v]).

(c) 7-Methoxy-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione

To 7-methoxy-10,11-dihydrodibenzo[b,f][1,4] thiazepin-11-one (0.5g, 1.95mmol) in pyridine (10ml) was added phosphorus pentasulphide (0.58g, 0.675 equivalents) and the mixture was heated under reflux for 3.5 hours. The mixture was cooled and the pyridine was removed under reduced pressure, the residue washed with water and recrystallised from methanol to give the title compound as a yellow solid (0.38g, m.p. 239 - 241°, Rf 0.85 [silica, cyclohexane/ethyl acetate (1:1, v/v)].

Example 11

7-Methoxy-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione-5,5-dioxide

(a) 7-Methoxy-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one-5,5-dioxide

To 7-methoxy-10,11-dihydrodibenzo[b,f][1,4] thiazepin-11-one (1g, 3.89mmol) in acetic acid (15ml) was added sodium perborate (2.4g, 4 equivalents) and the mixture was heated under reflux for 5 hours. On cooling the perborate was filtered off, the acetic acid was removed under reduced pressure to give a white solid which was washed with water and recrystallised to give the title compound as a white solid (0.8g, m.p. 244 - 246°, Rf 0.59 [silica, cyclohexane/ethyl acetate, 1:1 v/v]).

(b) 7-Methoxy-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-thione-5,5-dioxide

To 7-methoxy-10,11-dihydrodibenzo[b,f][1,4]thiazepin-11-one-5,5-dioxide (0.6g, 2.07mmol) in pyridine (5ml) was added phosphorus pentasulphide (0.62g, 0.675 equivalents) and the mixture was heated under reflux for 6 hours. On cooling, the pyridine was removed under reduced pressure, the residue obtained was washed with water, 3% HCl-brine and recrystallised from methanol to give the title compound (0.5g, m.p.250 - 252°, Rf 0.5 [silica, cyclohexane/ethyl acetate (1:1, v/v)].

Antiviral activity for compounds according to the invention can be demonstrated in vitro against HIV (MT4 assay) and in the HeLa-CD4$^+$ plaque reduction assay. Results for a selection of the compounds of he invention are shown in the following table.

Compound of Example No.	HIV (in vitro) MT4 IC_{50} (1m)	HeLa-CD4
3	9	5
6	44.4	14.4
8(iv)	3.3	15.4

Examples

The following examples illustrate pharmaceutical formulations according to the invention to which the active ingredient is a pharmaceutically acceptable compound according to the invention.

Example 12

Tablet Formulations

The following formulations A, B and C are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of the magnesium stearate and compression.

Formulation A

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Povidone B.P.	15	9
(d)	Sodium Starch Glycollate	20	12
(e)	Magnesium Stearate	5	3
		500	300

Formulation B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose	150	-
(c)	Avicel PH 101	60	26
(d)	Povidone B.P.	15	9
(e)	Sodium Starch Glycollate	20	12
(f)	Magnesium Stearate	5	3
		500	300

Formulation C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium stearate	4
	359

The following formulations, D and E, are prepared by direct compression of the admixed ingredients.

Formulation D

	mg/capsule
Active Ingredient	250
Pregelatinised Starch NF15	150
	400

Formulation E

	mg/capsule
Active Ingredient	250
Lactose	150
Avicel	100
	500

Formulation F (Controlled Release Formulation)

The formulation is prepared by wet granulation of the following ingredients with a solution of povidone followed by addition of the magnesium stearate and compression.

	mg/tablet
(a) Active Ingredient	500
(b) Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c) Lactose B.P.	53
(d) Povidone B.P.C.	28
(e) Magnesium Stearate	7
	700

Drug release takes place over a period of about 6-8 hours and is complete after 12 hours.

Example 13

Capsule Formulations

Formulation A

A capsule formulation is prepared by admixing the ingredients of Formulation D in Example 3 above and filling into two-part hard gelatin capsule.

Formulation B

	mg/capsule
(a) Active ingredient	250
(b) Lactose B.P.	143
(c) Sodium Starch Glycollate	25
(d) Magnesium Stearate	2
	420

Capsules are prepared by admixing the above ingredients and filling into two-part hard gelatin capsules.

Formulation C

	mg/capsule
(a) Active ingredient	250
(b) Macrogol 4000 BP	350
	600

Capsules are prepared by melting the Macrogol 4000 BP, dispersing the active ingredient in the melt and filling the melt into two-part hard gelatin capsules.

Formulation D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

Formulation E (Controlled Release Capsule)

The following controlled release capsule formulation is prepared by extruding ingredients (a), (b) and (c) using an extruder, followed by spheronisation of the extrudate and drying. The dried pellets are then coated with the release-controlling membrane (d) and filled into two-piece, hard gelatin capsules.

	mg/capsule
(a) Active Ingredient	250
(b) Microcrystalline Cellulose	125
(c) Lactose BP	125
(d) Ethyl Cellulose	13
	513

Example 14

Injectable Formulation

Formulation A

Active ingredient	0.200g
Hydrochloric acid solution, 0.1M	q.s. to pH 4.0 to 7.0
Sodium hydroxide solution, 0.1M	q.s. to pH 4.0 to 7.0
Sterile water	q.s. to 10ml

The active ingredient is dissolved in most of the water (35°-40°C) and the pH adjusted to between 4.0 and 7.0 using the hydrochloric acid or the sodium hydroxide as appropriate. The batch is then made up to volume with the water and filtered through a sterile micropore filter into a sterile amber glass vial 10ml and sealed with sterile closures and overseals.

Formulation B

Active ingredient	0.125 g
Sterile, pyrogen-free, pH 7 phosphate buffer,	q.s. to 25 ml

Example 15

Intramuscular injection

Active Ingredient		0.20 g
Benzyl Alcohol		0.10 g
Glycofurol 75		1.45 g
Water for Injection	q.s. to	3.00 ml

The active ingredient is dissolved in the glycofurol. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile amber glass vials 3 ml.

Example 16

Syrup

Active ingredient		0.25 g
Sorbitol Solution		0.10 g
Glycerol		2.00 g
Sodium Benzoate		0.005 g
Flavour, Peach 17.42.3169		0.0125 ml
Purified Water	q.s. to	5.00 ml

The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbitol solution and finally the flavour. The volume is made up with purified water and mixed well.

Example 17

Suppository

	mg/suppository
Active Ingredient	250
Hard Fat, BP (Witepsol H15 - Dynamit Nobel)	1770
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 lm sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250 lm stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C, 2.0g of the mixture is filled into suitable, 2 ml plastic moulds. The suppositories are allowed to cool to room temperature.

Example 18

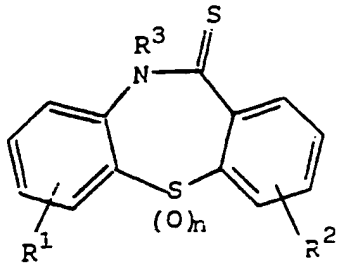
Pessaries

	mg/pessary
Active ingredient	250
Anhydrate Dextrose	380
Potato Starch	363
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by direct compression of the resulting mixture.

CLAIMS:

1. Compounds of formula (I)



(I)

wherein:

n is 0, 1 or 2; and

R^1 and R^2, which may be the same or different, each represent one or more ring substituent(s) selected from:

hydrogen, hydroxy, halogen, cyano, nitro, C_{1-6}alkyl, C_{3-6}cycloalkyl or C_{1-6}alkoxy (where the alkyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen atoms and hydroxyl groups);

$-NR^4R^5$ where R^4 and R^5, which may be the same or different, each represent hydrogen or C_{1-6}alkyl;

$-S(O)_mR^6$, where m is 0, 1, 2 or 3 and R^6 represents hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

$-SO_2NR^4R^5$ where R^4 and R^5 are each as defined above;

phenyl, phenylC_{1-3}alkoxy or phenylC_{1-3}alkyl where the phenyl group may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, nitro, halogen and amino; and

$-CO_2H$ or $-COR^7$ where R^7 is C_{1-6}alkyl or C_{3-6}cycloalkyl;

R^3 represents hydrogen or C_{1-4}alkyl;

or an ester, salt or other physiologically functional derivative thereof,

for use in therapy.

2. Compounds according to Claim 1 for use as an antiviral agent.

3. Compounds according to Claim 1 or 2 wherein R3 is hydrogen.

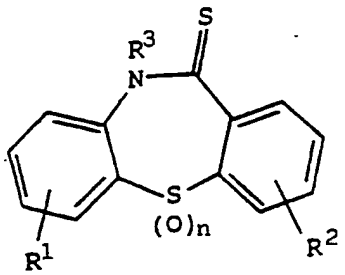
4. Compounds according to Claim 1 or 2 wherein R3 is C1-4alkyl.

5. Compounds according to any of Claims 1 to 4 wherein R^1 and R^2, which may be the same or different, each represent hydrogen or a ring substituent selected from halogen; nitro; C_{1-6}alkyl; C_{1-6}alkoxy, haloC_{1-6}alkyl, $-NR^4R^5$ (where R^4 and R^5, which may be the same or different, each represent hydrogen or C_{1-6}alkyl); $-SO_3H$; phenyl; phenylC_{1-3}alkyl; or $-CO_2H$.

6. Compounds according to Claim 1 or 2 selected from
dibenzothiazepin-11(10H)-thione;
dibenzothiazepin-11(10H)-thione-5,5-dioxide;
3-trifluoromethyldibenzothiazepin-11(10H)-thione;
3-trifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
4-trifluoromethyldibenzothiazepin-11(10H)-thione;
4-trifluoromethyldibenzothiazepin-11(10H)-thione-5-oxide;
4-trifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
7-methoxydibenzothiazepin-11(10H)-thione;
7-methoxydibenzothiazepin-11(10H)-thione-5,5-dioxide;
8-trifluoromethyldibenzothiazepin-11(10H)-thione;
8-trifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
4-trifluoromethyl-9-methyldibenzothiazepin-11(10H)-thione;
4-trifluoromethyl-9-methyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
10-ethyl-3-trifluoromethyldibenzothiazepin-11(10H)-thione;
4-fluorodibenzothiazepin-11(10H)-thione;
4-fluorodibenzothiazepin-11(10H)-thione-5,5-dioxide;
10-methyl-4-fluorodibenzothiazepin-11-thione;
10-methyl-4-trifluoromethyldibenzothiazepin-11-thione;

4-methylthiodibenzothiazepin-11(10H)-thione;
4-methylthiodibenzothiazepin-11(10H)-thione-5,5-dioxide;
2-aminodibenzothiazepin-11(10H)-thione;
2-nitrodibenzothiazepin-11(10H)-thione;
2-nitrodibenzothiazepin-11(10H)-thione-5,5-dioxide;
4,8-bistrifluoromethyldibenzothiazepin-11(10H)-thione;
4,8-bistrifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
1-methoxydibenzothiazepin-11(10H)-thione;
1-methoxydibenzothiazepin-11(10H)-thione-5,5-dioxide;
1-fluorodibenzothiazepin-11(10H)-thione;
methyl dibenzothiazepin-11(10H)-thione-3-carboxylate;
dibenzothiazepin-11(10H)-thione-3-carboxylic acid; and esters, salts and other physiologically functional derivatives thereof.

7. Compounds of formula (I)



(I)

wherein:

n is 0, 1 or 2; and

R^1 and R^2, which may be the same or different, each represent one or more ring substituent(s) selected from:

hydrogen, hydroxy, halogen, cyano, nitro, C_{1-6}alkyl, C_{3-6}cycloalkyl or C_{1-6}alkoxy (where the alkyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from halogen atoms and hydroxyl groups);

$-NR^4R^5$ where R^4 and R^5, which may be the same or different, each represent hydrogen or C_{1-6}alkyl;

$-S(O)_mR^6$, where m is 0, 1, 2 or 3 and R^6 represents hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

$-SO_2NR^4R^5$ where R^4 and R^5 are each as defined above;

phenyl, phenylC_{1-3}alkoxy or phenylC_{1-3}alkyl where the phenyl group may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, nitro, halogen and amino; and

$-CO_2H$ or $-COR^7$ where R^7 is C_{1-6}alkyl or C_{3-6}cycloalkyl;

R^3 represents hydrogen or C_{1-4}alkyl; with the proviso that when R^3 is hydrogen and n is zero, then at least one ring substituent R^1 or R^2 is other than hydrogen and that when there is only a single ring substituent R^1 or R^2 other than hydrogen then this substituent is not a chlorine atom in the 2-, 7-, or 8-position; or an ester, salt or other physiologically functional derivative thereof.

8. Compounds according to Claim 7 with the additional proviso that when R^3 is hydrogen and n is zero, then:

(1) at least one ring substituent R^1 or R^2 is other than hydrogen;

(2) when there is only a single ring substituent R^1 or R^2 other then hydrogen this is not a chlorine atom in the 2-, 7-, or 8-position;

(3) when there are two ring substituents R^1 and R^2, these are not: (i) R^1 = 8-chloro; R^2 = 2-chloro; or (ii) R^1 = 7-iodo; R^2 = 3-dipropylamino.

9. Compounds according to Claim 7 wherein:

n is 0, 1 or 2; and

R^1 and R^2, which may be the same or different, each represent one or more ring substituent(s) selected from:

hydrogen, hydroxy, cyano, C_{1-6}alkyl or C_{3-6}cycloalkyl (where the alkyl or cycloalkyl moiety may be substituted by one or more substituents selected from halogen atoms and hydroxyl groups);

$-NHR^4$ where R^4 represents C_{1-6}alkyl;

R^1 and R^2, which may be the same or different, each represent one or more ring substituent(s) selected from:

hydrogen, hydroxy, cyano, C_{1-6}alkyl or C_{3-6}cycloalkyl (where the alkyl or cycloalkyl moiety may be substituted by one or more substituents selected from halogen atoms and hydroxyl groups);

$-NHR^4$ where R^4 represents C_{1-6}alkyl;

$-S(O)_mH$, where m is 0, 1 or 2, or $-SO_3R^6$ where R^6 represents hydrogen, C_{1-6}alkyl or C_{3-6}cycloalkyl;

$-SO_2NR^4R^5$ where R^4 and R^5 are each as defined above;

phenyl, phenylC_{1-3}alkoxy or phenylC_{1-3}alkyl where the phenyl group may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, nitro, halogen and amino; and

$-CO_2H$ or $-COR^7$ where R^7 is C_{1-6}alkyl or C_{3-6}cycloalkyl;

R^3 is hydrogen or C_{1-4}alkyl;

with the provisos that when R^3 is hydrogen, then at least one ring substituent R^1 or R^2 is other than hydrogen;

or an ester, salt or other physiologically functional derivative thereof.

10. Compounds according to any of Claims 7 to 9 wherein R^3 is hydrogen.

11. Compounds according to any of Claims 7 to 9 wherein R^3 is C_{1-4}alkyl.

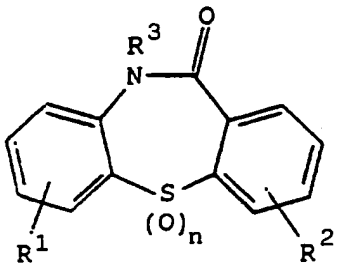
12. Compounds according to any of Claims 7 to 11 wherein R^1 and R^2, which may be the same or different, each represent hydrogen or a ring substituent selected from halogen, nitro, C_{1-6}alkyl; C_{1-6}alkoxy; haloC_{1-6}alkyl; $-NR^4R^5$ (where R^4 and R^5, which may be the same or different, each represent hydrogen or C_{1-6}alkyl); $-SO_3H$; phenyl; phenylC_{1-3}alkyl; or -CO2H, with the proviso that when R3 represents hydrogen then R^1 or R^2 do no both represent hydrogen.

3-trifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
4-trifluoromethyldibenzothiazepin-11(10H)-thione;
4-trifluoromethyldibenzothiazepin-11(10H)-thione-5-oxide;
4-trifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
7-methoxydibenzothiazepin-11(10H)-thione;
7-methoxydibenzothiazepin-11(10H)-thione-5,5-dioxide;
8-trifluoromethyldibenzothiazepin-11(10H)-thione;
8-trifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
4-trifluoromethyl-9-methyldibenzothiazepin-11(10H)-thione;
4-trifluoromethyl-9-methyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
10-ethyl-3-trifluoromethyldibenzothiazepin-11(10H)-thione;
4-fluorodibenzothiazepin-11(10H)-thione;
4-fluorodibenzothiazepin-11(10H)-thione-5,5-dioxide;
10-methyl-4-fluorodibenzothiazepin-11-thione;
10-methyl-4-trifluoromethyldibenzothiazepin-11-thione;
4-methylthiodibenzothiazepin-11(10H)-thione;
4-methylthiodibenzothiazepin-11(10H)-thione-5,5-dioxide;
2-aminodibenzothiazepin-11(10H)-thione;
2-nitrodibenzothiazepin-11(10H)-thione;
2-nitrodibenzothiazepin-11(10H)-thione-5,5-dioxide;
4,8-bistrifluoromethyldibenzothiazepin-11(10H)-thione;
4,8-bistrifluoromethyldibenzothiazepin-11(10H)-thione-5,5-dioxide;
1-methoxydibenzothiazepin-11(10H)-thione;
1-methoxydibenzothiazepin-11(10H)-thione-5,5-dioxide;
1-fluorodibenzothiazepin-11(10H)-thione;
methyl dibenzothiazepin-11(10H)-thione-3-carboxylate;
dibenzothiazepin-11(10H)-thione-3-carboxylic acid; and esters, salts and other physiologically functional derivatives thereof.

14. A pharmaceutical composition for the treatment of a viral infection which comprises at least one compound of formula (I) as defined in any of Claims 1 to 6 or an ester, salt or other physiologically functional derivative thereof, together with at least one physiologically acceptable carrier or excipient.

15. A method of treatment of a human or animal subject suffering from or liable to suffer from a viral infection which comprises administering to the said subject an effective amount of a compound of formula (I) as defined in any of Claims 1 to 6 or an ester, salt or other physiologically functional derivative thereof.

16. A process for the preparation of compounds of formula (I) as defined in any of Claims 1 to 6 which comprises: (A) reaction of a thiazepinone of formula (II)



(II)

with a thionating agent; or (B) for the production of compounds in which n is 1 or 2, treating the corresponding compound in which n is zero with an oxidising agent; or (C) for the production of compounds in which R^3 is C_{1-4}alkyl, treating the corresponding compound in which R^3 is hydrogen with an alkylating agent; and when the compound of formula (I) is obtained as a mixture of optical or geometric isomers optionally resolving the mixture to obtain the desired isomer; and/or optionally converting the compound of formula (I) produced into an ester, salt or other physiologically functional derivative.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/00804

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 281/16 A 61 K 31/55

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

	Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
1	X	EP,A,0419861 (BOEHRINGER INGELHEIM PHARMACEUTICALS et al.) 3 April 1991, see page 2, line 42 - page 3, line 40 ---	1-5,7-12,14,15
2	A	Collection of Czechoslovak Chemical Communications, vol. 48, no. 5, May 1983, Prague, CS, Z. POLIVKA et al.: "13-(4-Methylpiperazino)dibenzo[b,f]-1,2,4-triazolo[4,3-d]-1,4-thiazepine and its 6-chloro and 12-chloro derivatives; synthesis and pharmacology", pages 1465-1476, see compounds IIIa-c -----	8

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20-07-1992	19.08.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

:rnational application No.
PCT/GB92/00804

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 15 is directed to a method of treatment of the human or animal body (Rule 39.1(iv)PCT), the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200804 SA 58994

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 07/08/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0419861	03-04-91	AU-A- 6191690	07-03-91
		CA-A- 2024040	01-03-91
		JP-A- 3163021	15-07-91